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Mental Disorders and Coronary Heart Disease Risk: Could the Evidence Elude Us While We Sleep?

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Editorial; mental disorder; coronary heart disease risk; sleep; psychology and behavior

While provocative findings from large epidemiological studies suggest that mental disorders and/or elevated psychiatric symptoms are independent risk factors for the incidence and recurrence of coronary heart disease (CHD), other studies do not replicate this somewhat startling finding.^{1–3} This research has been characterized by incomplete adjustment for confounders, by wide variation in the assessment of mental disorders, and by inconsistent inclusion of multiple mental disorders and overlapping symptom clusters. For incident CHD, the most convincing evidence comes from prospective studies linking a diagnosis of depression or the presence of elevated depressive symptoms with later occult CHD.³ And, although there have been tantalizing glimpses of associations of other types of mental disorders, such as alcohol/substance-use disorder, anxiety, and schizophrenia, with incident CHD, there are a paucity of studies examining this risk. Indeed, we conducted a preliminary search of the prospective epidemiological literature on the association of mental disorders with incident CHD and found that out of 123 results retrieved, approximately 60% focused uniquely on depression, 10% on alcohol/substance use disorder, 11% on anxiety or posttraumatic stress disorder (PTSD), and 14% on psychosis or schizophrenia. Thus, outstanding questions about the nature and consistency of the association of specific types of mental disorders--other than depression--and incident CHD remain.

In this issue of *Circulation*, Gale et al. provide results from a cohort of over 1 million adult men born in Sweden from 1950–1976 who were followed for 22 years for incident CHD⁴. Importantly, all were systematically assessed at conscription (around 18 years) for multiple psychiatric disorders by trained psychiatrists, including alcohol-related disorders, other non-affective psychoses, schizophrenia, bipolar disorder, depressive disorder, neurotic disorders, adjustment disorders, personality disorders, and other substance use disorders. This is one of the first and largest population-based studies with such a comprehensive assessment of mental disorders that adequately accounted for secular time trends and potential confounders. Interestingly, Gale et al. showed that men who were diagnosed with any early onset mental disorder or who had a psychiatric hospitalization during the follow-up period of 22 years had an increased risk of incident CHD even after adjustment for numerous confounders. Of note, those with a depressive disorders diagnosis in early adulthood were only at marginally increased CHD risk after adjustment for standard CHD risk factors, and adjustment for potential explanatory variables such as socioeconomic status, IQ, and risky alcohol intake. Although the study by Gale and colleagues is impressive and provides

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evidence of heightened incident CHD risk among those with mental disorders, we highlight for readers some issues that warrant consideration in understanding mental disorders and cardiovascular risk.

First, the study by Gale and colleagues was conducted in Sweden, a country that has a single payer system, with no apparent disparities in mental and physical health reimbursements.⁵ This is in sharp contrast to the United States health care system, where reimbursements for mental health or behavioral services are not quite on par with reimbursements for physical health services, despite several recent policy changes.⁶ Further, these two high-income countries differ markedly in the degree of income inequality and national health profiles, with the US faring much worse in national health status indicators despite a high level of per capita spending on health care.⁷ Thus, the extent to which the findings from Sweden should be accepted as representative of the influence of mental disorders on CHD risk in the United States is unclear. It is also possible that disparities in mental health services will result in under-treatment of those with mental disorders, particularly those from disadvantaged groups, which in turn would accentuate CHD risk among these subgroups. Also Gale and colleagues focused exclusively on men, so the extent to which these findings can be generalized to women is unclear. We cannot assume that risk factors for CHD operate the same for men and women.⁸

Next, we have to caution readers that there are many potential explanations left to be explored, before concluding that this association might be causal. For example, it is quite possible that cardiotoxic side effects associated with the use of typical and atypical antipsychotic medications that block repolarizing potassium currents in vitro and prolong the QT interval, might explain the increased CHD risk among those diagnosed with mental disorders.⁹ Similarly, metabolic effects of psychotropic medication use might be key contributors of increased CHD risk through weight gain.¹⁰ Other explanations for this observed correlation include the presence of the S allele of the serotonin transporter (5-HTT) gene-linked polymorphic region, which increases the risk for both depression and CHD risk.¹¹ Other potential intriguing explanations include the undiagnosed presence of supraventricular tachycardias, which are mistakenly experienced as anxiety or panic symptoms by patients. One final example of a possible common cause for this association is the illicit use of cocaine, which is known to cause both coronary vasospasm and early CHD, as well as paranoia, panic, and lasting anxiety disorders.

Ultimately, the question often left unanswered by these large and sophisticatedly designed epidemiological studies is *why*, or *what explains the excess risk conferred by mental disorders*? By and large, the last 20 years have witnessed an exponential growth in research to identify the specific mechanisms linking mental disorder to CHD risk. Although several biological and behavioral mechanisms have been proposed to explain the association between mental disorder and CHD,¹² with the majority focused on the understanding the depression – CHD link, so far, we have come up empty handed. Examples of the biological mechanisms proposed to explain the depression-CHD association include platelet reactivity, inflammation, autonomic imbalance, sleep architecture disruption, circadian rhythm disruption anabolic/catabolic hormonal imbalance, and many others.¹³ However, we have little direct human evidence that any of these are causally implicated in the pathogenesis associated with mental disorders that precede incident CHD. Mental disorders might also influence CHD risk through its effects on a patients' behaviors, such as weight gain¹⁴ (even independent of that potentially caused by psychotropic medication use), smoking, or other CHD accelerating risks, such as non-adherence to a medication regimen¹⁵ and/or to other lifestyle recommendations.¹⁶ Indeed, it is reasonable to expect that a patient with a mental disorder will have low compliance with preventive cardiology recommendations.¹⁵ In addition, there may be disparities in the way the healthcare system behaves towards patients

with mental disorders, and these differences - for example, the treatment they receive - may lead to worse outcomes.¹⁷ More likely is these systemic, biological and behavioral mechanisms interact with one another in a complex system with positive and negative feedback mechanisms.

We have recently been intrigued by one specific behavior that we all engage in that could be implicated in the complicated connections between mental disorders and cardiovascular risk: sleep. Over 30% of our adult lives will be spent asleep, yet most of the mechanistic research on mental health and cardiovascular risk has focused on activities, behaviors, and biological processes that occur while awake. For example, while sleep disturbances, such as short sleep duration, and obstructive sleep apnea are associated with incident CHD,^{18, 19} only a handful of studies have examined if this particular mechanism is implicated in the relation of mental disorders with CHD risk. This dearth exists, despite extensive research on the intimate connection and bidirectionality of sleep disturbances and mental disorders such as depression.²⁰ Chronic sleep disturbances lead to sleep architecture disruption and circadian rhythm disruption, which in turn might increase risk for CHD through the disruptions that occur for endothelial function, inflammatory regulation, and/or metabolic regulation, among other suggested pathways.²¹

Clinicians and scientists have observed the heightened risk for CHD among those with a mental disorder since 1937.²² We have literally thousands of documented observations about this increased risk, but we remain in doubt about the causal status of this risk marker, the culprit mechanisms if mental disorders are indeed a causal risk factor, and the treatments needed to prevent this CHD risk. In light of the evidence reviewed, and this new, large, population-based, observational finding reported in this issue of *Circulation*,⁴ the next logical question becomes: *What should practicing preventive cardiologists do?* We offer three suggestions. First, the existing observational evidence-base on mental disorders and CHD risk strongly indicate that a greater focus on and assessment of established behavioral risk factors for CHD such as smoking and physical inactivity, that often co-occur with mental disorders, would be in the best interest of these patients. Second, cardiologists should expect greater difficulties with any medication adherence among these patients, and aggressive management of medication use should be pursued. Care providers should be particularly on alert for QT prolongation among patients taking typical and atypical antipsychotic medications and increased metabolic risks associated with rapid and steadily increasing weight gain from use of these and other psychotropic medications over time. Finally, we wish we could urge preventive cardiologists to consider that sleep disturbances might exacerbate both of the problems noted above—poor CHD risk management and poor medication adherence that is to be expected in these patients. However, we have so little data on the impact of sleep, or sleep disorders, on the CHD risk level, or the later behaviors of these patients, such as overeating, that we cannot yet make this suggestion. We know that mental disorders mark a 20% to 80% increase in incident CHD risk and death. We don't yet have the research or the tools to effectively know why, and what to do about this puzzling association. Perhaps its time to consider a more complex systems approach to CHD risk identification in patients with mental disorders that focuses on processes that occur while asleep.

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